The CENTRAL AFRICAN JOURNAL OF MEDICINE

Vol. 4. No. 10. OCTOBER, 1958.

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PUBLISHED MONTHLY, ANNUAL SUBSCRIPTION £2 2s. 0d.

Registered at the General Post Office as a Newspaper.

The Central African
Journal of Medicine

Volume 4 OCTOBER, 1958 No. 10

Porphyria in Africa

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Until recently, porphyria has been regarded as a rare condition in most countries and has merited but passing comment in standard textbooks of medicine. As this is a condition requiring a high index of diagnostic suspicion, it seems a useful task to present the common features of the disorder as seen in Europeans and Africans, to comment on the procedures necessary for diagnosis and to speculate on the factors precipitating its onset. It is becoming increasingly apparent that porphyria occurs frequently in South and Central Africa, both amongst those of European and African stock. As in other countries, the increase in diagnosis is due to the wider knowledge of its clinical manifestations and to the combined interest of both clinicians and biochemists. Since Barnes (1945) first described a series of South African cases, several of whom were African, the number reported has multiplied rapidly. Porphyria has now been found in all parts of South Africa and more recently in Central Africa, where Gelfand (1955 and 1956) has described cases seen in Southern Rhodesia. A case of acute porphyria has been described in a West African in England; in the Sudan, congenital porphyria has been reported in siblings and from Dakar a child of ten with hepatic porphyria has recently been reported. No cases have as yet been reported from any of the East African territories.

Structure, Biosynthesis and Excretion

Precise classification, rational investigation and treatment of this disorder can only be achieved by some understanding of the biosynthesis and excretion of the porphyrins and their abnormalities in disease. The porphyrins occur in both the plant and animal world and in both, porphyrin complexes mediate vital cellular processes. They are pigments composed of four pyrrole rings connected by four methane bridges to form a large ring structure, and they differ from one another in structure and properties, depending on the character of the substituent groups on the eight free corners of the four pyrrole nuclei (Fig. 1). Chlorophyll, essential for photosynthesis, is a magnesium-porphyrin compound and the structural relationship between chlorophyll and haem, an iron-porphyrin compound, is obvious. In the human body the release of energy from the products of photosynthesis depends on those porphyrin complexes which incorporate haem in their structure. These porphyrin complexes are known as respiratory enzymes and are responsible for the transport, storage and exchange of oxygen and are concerned with the oxidation of cellular constituents. It can be seen that from the initial fixation of solar energy in green plants to its eventual utilisation in man, porphyrins play a vital role.

Although many types of porphyrins have been synthesised and both uroporphyrin and coproporphyrin can theoretically exist in isomeric types I-IV, only two main isomers have so far been isolated in nature, Type I and Type III. Uroporphyrin and coproporphyrin are so designated because they were originally isolated from the urine and stools respectively; it has now been established that either or both may appear in the urine or faeces (Fig. 2).

In health, large amounts of Type III porphyrins are synthesised in the body and utilised for the formation of haemoglobin and the other respiratory factors, while only minute amounts are excreted. Very small quantities of Type I are also produced, apparently as a by-product of normal haematopoiesis; these serve no useful purpose and are excreted largely by the liver in the bile and eventually in the faeces and urine. In man, the combination of ferrous iron with protoporphyrin Type III constitutes the prosthetic group for the haem compounds, i.e., haemoglobin, myohaemoglobin, cytochromes, catalases, peroxidases and other respiratory enzymes. Primitive red cells contain porphyrins

rather than haemoglobin, the amount of porphyrin decreasing and haemoglobin increasing as the cell matures. Normal red blood cells still contain small amounts of protoporphyrin and traces of Type III coproporphyrin. The importance of the role played in metabolic processes by the respiratory enzymes is self-evident and makes it a shade easier to understand the widespread tissue damage which can take place in porphyria when the biosynthesis of these porphyrin substances is disturbed.

Normal Patterns of Excretion

Coproporphyrin I, representing the minor metabolic pathway is not used in the organism, and all that is formed is excreted in the urine, and via the bile, in the faeces. The major metabolic product, *coproporphyrin III,* is largely converted to protoporphyrin III. The minute amount (.05 per cent.) not converted is excreted in the urine, and via the bile, in the faeces. There appears to be a significant individual and geographical variation in the ratio of the urinary coproporphyrin isomers excreted; recent studies suggest that in children and adults the major part of the urinary coproporphyrin is Type III.

Uroporphyrin is excreted in the urine in small amounts, detectable only by very precise methods. However, in adults suffering from a wide variety of conditions mostly severe and potentially fatal (cirrhosis and leukaemia, barbiturate and alcohol addiction), uroporphyrin is excreted in amounts larger than the traces normally found, i.e., moderate uroporphyrinuria under such conditions is not evidence of an inborn metabolic error. The metabolic error which exists in porphyria is a quantitative rather than a qualitative one, and it is excessive uroporphyrin excretion which is characteristic of porphyria.

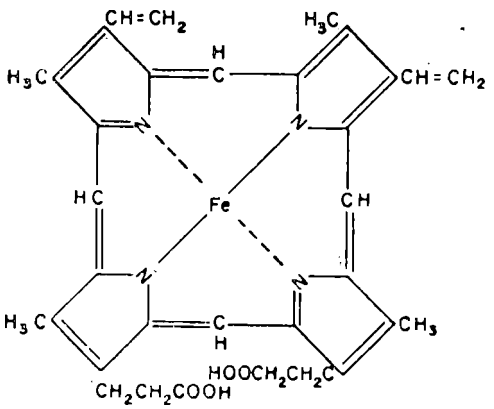
Porphobilinogen, a colourless non-fluorescent monopyrrole precursor of uroporphyrin, is not normally present in the urine, but is characteristically present in those cases of acute porphyria with abdominal pain and/or neurological disturbances.

Thus the abnormal types of porphyrin excretion which we see in porphyria reflect defective porphyrin synthesis, an imbalance in the chain of events depicted in Fig. 2.

Haematoporphyrinuria.—This term is frequently used but is obsolete, as this substance is a purely "laboratory" product which does not occur in nature.

Porphyrinuria.—This term designates an increase in the amount of urinary porphyrins without regard to the type of porphyrins present. The definition as such permits porphyria to be called a porphyrinuria, but in common and accepted usage the term porphyria is applied only to those individuals excreting excessive amounts of uroporphyrins and/or porphobilinogen. In a large number of conditions there is an increased urinary coproporphyrin excretion, and it is these which are commonly termed

HAEM



CHLOROPHYLL

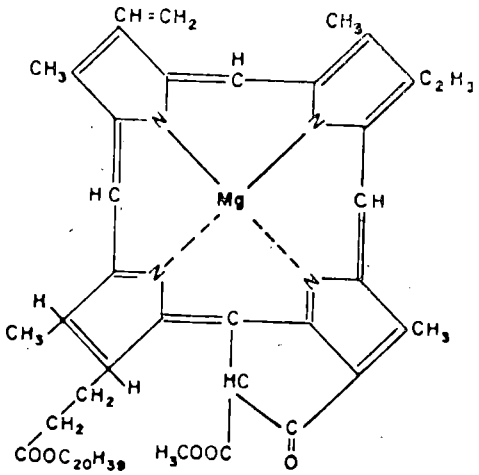


FIGURE 1

porphyrinurias or, more correctly, secondary coproporphyrinurias (Table I).

Table I

PORPHYRINURIAS

(Secondary Coproporphyrinuria)

COPROPORPHYRIN I	COPROPORPHYRIN III
Acute febrile states (pneumonia, lung abscess).	Rheumatic fever, poliomyelitis.
Infective hepatitis, Non-alcoholic cirrhosis.	Alcoholic cirrhosis, acute alcoholism.
Obstructive jaundice.	Hodgkin's disease.
Pernicious and haemolytic anaemias, leukaemia.	Iron-deficiency anaemia, aplastic anaemia.
	Lead poisoning.

Mention is only made of these conditions in order to show what is not porphyria and to discourage the inexact use of the term porphyrinuria.

Idiopathic Coproporphyrinuria.—Occasional individuals exhibit a physiological coproporphyrinuria III. This is an asymptomatic condition with no history or signs of exposure to infections, chemical poisons or other agents likely to lead to coproporphyrinuria. Adults are mainly affected and it is usually not familial, although cases of hereditary coproporphyrinuria have been recently described.

The definitive diagnosis of porphyria is established by the demonstration by qualitative means of uroporphyrin or of the colourless chromogen porphobilinogen in the urine.

It should be remembered that patients with porphyria may at times excrete no porphyrins in their urine and that the quantity excreted at different times varies very greatly. Negative tests in a clinically suspect case do not exclude the diagnosis, and repeated examinations should be made.

The Human Porphyrias

These are inborn errors of metabolism, characterised by the excretion of large amounts of uroporphyrin and/or porphobilinogen. In recent years the understanding of the porphyrias

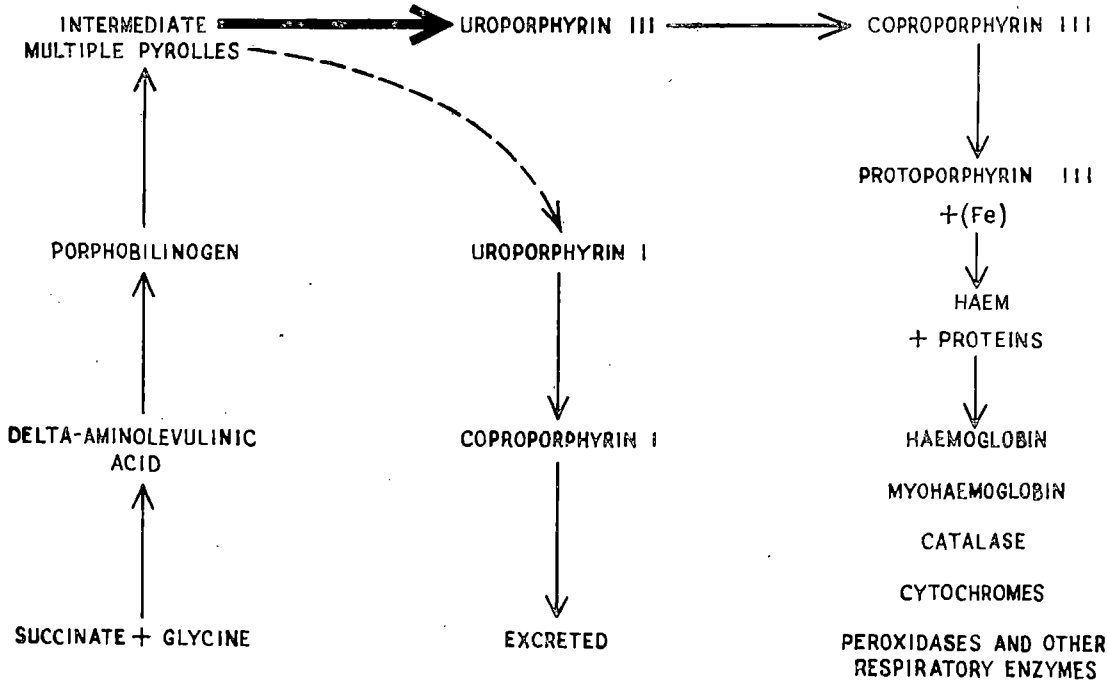


FIGURE 2. SYNTHESIS OF PORPHYRINS AND HAEM COMPOUNDS

has undergone significant changes, and while controversy still exists regarding classification, it is now widely accepted that the disease can be divided into two principal categories based on the site of origin of the abnormal porphyrins (Watson *et al.*, 1951).

1. *Erythropoietic Porphyria*—
   (Congenital; photosensitive.)
2. *Hepatic Porphyria*—
   (a) Acute intermittent.
   (b) Chronic cutaneous (*Cutanea tarda*).
   (c) "Mixed."
   (d) Latent.

Erythropoietic Porphyria.

The disorder is essentially one concerning the synthesis of haemoglobin from porphyrins, and the metabolic defect is located in the developing normoblasts of the bone marrow where excessive amounts of uroporphyrin I and coproporphyrin I are formed and liberated. These porphyrins permeate the tissues and appear in high concentrations in the excreta. The high concentration of porphyrin in the normoblastic nuclei can be well shown by fluorescence microscopy.

Hepatic Porphyria.

In striking contrast to the erythropoietic type, the bone marrow and its porphyrin content are normal. The abnormality apparently resides in the liver where the enzyme catalase has been implicated, and liver disease or hepatic functional impairment can be demonstrated in a high proportion of cases. Fluorescence microscopy of the liver in the cutanea tarda type reveals large amounts of preformed uroporphyrins which fluoresce, while in the acute intermittent type there is relatively little fluorescence, but non-fluorescing porphobilinogen is readily demonstrated in considerable quantities in the liver. In the "mixed" types, varying transitions are noted and the ratio of fluorescing porphyrin to non-fluorescing precursor varies from time to time. In the hepatic porphyrias both urine and faeces contain excessive amounts of coproporphyrin, uroporphyrin and porphobilinogen. The uroporphyrin is present mainly as a zinc complex, whereas in the erythropoietic form it is mainly in the free state.

Inheritance in Porphyria.

The erythropoietic form of porphyria has been shown to be familial in exceptional cases only. It is probably inherited as a Mendelian recessive character, and despite attempts to prove that males are more frequently affected than females, there seems to be no fundamental sex difference in the incidence.

On the other hand, the hepatic forms are commonly familial, and if a careful search is made for latent or mild cases in the families of the patient the existence of the genetic trait is more often than not apparent. Dean and Barnes (1955) have demonstrated in a most fascinating study that in South Africans of European stock porphyria is inherited as a Mendelian dominant characteristic and is not sex-linked. Acute intermittent, cutanea tarda and latent forms may all occur in the one family, and in many cases one clinical type may turn into another. In Africans the familial incidence has been demonstrated in a few cases in South Africa, but the problem of tracing families is a more difficult task with a migrant labour force and it is likely that amongst the more urbanised African population familial tendencies will be more readily traced.

Since the early days of interest in this condition the term "toxic" has been used to imply that some cases were of an acquired nature due to the exhibition of toxic chemicals. While it cannot be questioned that hepatic porphyria is frequently precipitated by barbiturates, alcohol and other factors, it may well be that this has occurred in individuals with latent porphyria previously free of symptoms. Indeed, it has been frequently demonstrated that these drugs may precipitate clinical attacks in persons with known latent porphyria identified because their relatives had manifest clinical signs of the disease. It seems "not proven" that any of these drugs or procedures are capable of producing porphyria *de novo*, and the existence of acquired or "toxic" porphyria is questionable.

Clinical Features of the Porphyrias as Seen in Europeans

A. *Erythropoietic.*

This is a very rare condition, comprising about 2 per cent. of all the porphyrias. The term congenital is unsatisfactory, for although the trait is certainly present at birth, in a number of cases the symptoms fail to appear until several years after birth. There is usually, however, an early onset and red urine may be noticed on the nappies. In most cases the condition is not apparent until the child becomes more exposed to sunlight. Uroporphyrin I has been shown to have marked photodynamic

activity and is almost certainly responsible for the lesions in this type of porphyria.

Skin Lesions.—Exposure to sunlight is followed by erythema and/or extensive bullous eruptions, which become pustular, leave shallow ulcers and heal slowly with crusting, pigmentation and depigmentation and the development of shallow scars. This skin condition is known as hydroea aestivale and it can also occur in non-porphyric subjects. In porphyria, however, extensive mutilation can occur with loss of fingers, portions of the nose and ears, scarring and loss of elasticity about the cheeks and mouth, and scarring of the conjunctiva and cornea with resultant blindness. These effects are not seen in non-porphyric hydroea aestivale. The end-results must be distinguished from advanced xeroderma pigmentosa, scleroderma and leprosy, it being of interest to note that the first African case of congenital porphyria was referred from a leprosy institution. Hirsutism is common, and while not usually extensive, a "bearded lady" with congenital porphyria has been described. The deciduous teeth are usually stained a reddish-brown or lavender colour by deposits of porphyrin in the tooth substance; even when the teeth are not obviously discoloured, they will fluoresce a bright red under ultra-violet light. The spleen is usually moderately enlarged and a haemolytic process is nearly always present, associated with a reticulocytosis and a normoblastic hyperplasia of the bone-marrow. Studies suggest that the abnormality responsible for the haemolytic process is an intracorpuscular one. In some cases splenectomy has been followed by an improvement in the haemolytic process and also in the photosensitivity. It seems that splenectomy by eliminating the increased haemolytic activity has produced a reduced erythropoiesis and hence a reduction in porphyrin formation, which in turn accounts for the reduced photosensitivity. The urine varies from pink to port wine to black, depending on the concentration of the porphyrins and the state of oxidation, and both urine and stools contain large amounts of uro- and coproporphyrin I, but no porphobilinogen. Bone-marrow porphyrin levels are greatly elevated, while the liver contains normal or very slightly raised concentrations.

The prognosis in these cases is not altogether gloomy, and although scarring and deformity are the most spectacular aspects, it is anaemia and intercurrent infections which cause death. Treatment is usually directed to the prevention of the effects of photosensitivity and control of the haemolysis. Para-amino benzoic acid cream has been used to protect the skin, and in some cases splenectomy has been successful in treating both the anaemia and the photosensitive lesions.

B. *Hepatic.*

This is the largest and most important group, comprising about 98 per cent. of all cases of porphyria. The relative incidence of the various sub-groups may differ according to the geography and race, e.g., in U.S.A. there are about three acute cases for every delayed cutaneous or mixed case, while among Africans in South Africa acute cases are extremely rare, the cutanea tarda type being seen almost exclusively. Functional impairment of the liver or established liver disease is often observed in this group, especially in the cutanea tarda and mixed types; it is not a particular feature of the acute intermittent variety. One cannot yet draw any conclusion about the relationship of the hepatic disturbance to the porphyria; in Europeans the strong familial incidence suggests that liver affection is secondary to the porphyria, while in Africans it remains a possibility that it may be an acquired condition secondary to liver disorder.

One feature common to all the types of hepatic porphyria is the *intermittency*, and mild attacks of the various manifestations are more common than the severe ones. The diagnosis must be considered in any unexplained abdominal pain, particularly if recurrent, and in obscure mental disturbances and neurological disorders, including coma, convulsions and peripheral neuropathy. Recurrent skin lesions or jaundice may uncommonly be the presenting features, and even in acute malignant hypertension the possibility of hepatic porphyria must be kept in mind (Case 1).

(1) *Acute Intermittent Porphyria.*

Females are affected twice as frequently as males and the condition is not usually manifest until the age of 20 or so. Most acute attacks are ushered in by abdominal pain (70 per cent.), mental (15 per cent.) or nervous (10 per cent.) manifestations. Acute attacks are often precipitated by drugs or surgical procedures; the exact mechanism by which this happens is not established. Although barbiturates are the best known, alcohol is a much more commonly incriminated agent, and rarely sulphonamides and other drugs are responsible.

(a) *Gastro-Intestinal Symptoms.*—Paroxysms of generalised abdominal colic are the most common manifestation. The pain can be ex-

cruciating, but little or no abdominal tenderness or rigidity occurs and it may radiate into the flanks or downwards into the groins. Frequently it is associated with severe constipation, commonly with nausea, vomiting and abdominal distension. The colic is certainly due to the painful spasm and dilatation of the bowel. Nearly all females with this condition bear the scars of frequent surgery and many of them have had their gall-bladders, ovaries or appendices removed in their search for relief from pain. A leucocytosis occurs in less than 10 per cent. of cases, but when present it can make diagnosis even more difficult than usual.

(b) *Central Nervous System.* — Typically, pains occur in the lower limbs and arms, followed by paraesthesiae, weakness and loss of deep reflexes and sensation. The findings are either those of a diffuse polyneuritis or a slowly ascending polyneuritis which may involve medullary centres causing bulbar paralysis. The resemblance to Guillan-Barré syndrome and to poliomyelitis can be marked and an abnormal cerebrospinal fluid is a not infrequent finding (30 per cent.). Sensory changes are generally mild. Cranial nerve involvement is usually evidenced by paresis of the vocal cords with hoarseness and occasionally by weakness of the ocular muscles. Episodic stupor and coma can occur, and epileptic attacks or atypical convulsions are very common, usually occurring in those who have already shown other manifestations of porphyria.

(c) *Hypertension* is common in acute attacks, sometimes preceding attacks of abdominal pain by several days and occasionally being prominent when paralysis is most marked. The hypertension is considered by some to be similar to that seen in bulbar poliomyelitis, as pathological changes have been noted in the reticular formation. E.C.G. changes have been noticed in association with the hypertension and are believed to be due to coronary artery spasm. Of these hypertensive patients, 27 per cent. have elevated blood urea levels irrespective of the height of the blood pressure.

(d) Although mental and emotional disturbances are considered to be of grave prognosis and to precede coma and death, this is certainly not invariable. Hallucinations are frequent when the C.N.S. involvement is severe and schizophrenic states are not uncommon, but complete and rapid recovery can occur from an apparently deep psychotic state. It is of interest to recall that Wäldenstrom found most of his cases of porphyria by a routine survey of the urine from patients in a Swedish mental hospital.

(e) Spasm of the retinal vessels may be seen, particularly during periods of hypertension, and temporary loss of vision has been reported.

(f) Tachycardia is very frequent during acute episodes, especially in the abdominal crises. However, bradycardia is not rare and has been a marked feature of one case which I have seen. This patient evidenced pulse rates of 40-60/minute during severe attacks of acute abdominal pain, the pulse rate returning to normal as the pain subsided.

(g) Hirsutism may be marked on exposed areas, usually in females, and diffuse pigmentation of the exposed parts is common.

(h) Electro-encephalograms: From a study of the tracings in four patients with acute porphyria over several years, we have shown (Shaper and Hughes, 1958) that during acute exacerbations there is a generalised theta and delta activity in proportion to the severity of the clinical manifestations of the cerebral damage. After frequent attacks permanent damage may result, leading to permanent changes in the E.E.G. and to histologically demonstrable changes in the central nervous system.

The Prognosis.—Acute attacks may prove fatal, ascending paralysis with respiratory failure being a not uncommon form of death. Mortality is high in those with nervous system manifestations, and probably 50 per cent. of these do not recover.

The Urine in Acute Intermittent Porphyria.—The urine may be normal in colour when passed, even during acute episodes, or it may merely look concentrated. If left in daylight for a few hours it becomes amber, particularly near the surface. Most cases, however, will have noticed a darkening of the colour at the outset of their disorder. The urine usually contains porphobilinogen, zinc complexes of uroporphyrin and coproporphyrin. Porphobilinogen is very rarely found, apart from porphyria, although Watson has described several such cases with liver disease (4), malignant disease (4), and bulbar polio, Guillain-Barré syndrome and bacterial endocarditis. These 11 cases have unfortunately led to the widespread belief that porphobilinogenuria is common in hepatic disease, malignant disease and any C.N.S. infection. It may well be that these cases all had latent porphyria. To complicate matters, in a recent survey of 80 cases seen at

the Mayo Clinic it was noted that no porphobilinogen was found in nine cases with severe C.N.S. involvement and in six cases with abdominal crises. In a further six cases no uroporphyrin was detected despite the presence of porphobilinogen and coproporphyrin. It should be emphasised that porphyrin excretions may be intermittent.

Case 1. Acute Intermittent Porphyria. Female aged 23 years.

In June, 1954, this patient noticed her urine was red in colour, and two months later she developed fever, constipation and lower abdominal pain, again associated with red urine. Within a few days she became confused and disorientated, complained of severe headache and blurred vision and then experienced two major epileptic attacks. On admission to hospital (August) she was febrile and wasted, B.P. 150/110. Blood urea was 110 mg. per 100 ml. Optic fundi normal and the brownish-red urine contained no protein or deposit. A few days later she collapsed in the ward and was found to be acutely hallucinated. Diagnosed as a "depressive state with schizophrenic symptoms," she was transferred to a mental hospital (September, 1954). Here she was found to be drowsy and restless, her speech was slurred and she complained bitterly of pains and paraesthesiae all over the body. Bilateral papilloedema was noted, B.P. 170/120 and the blood urea rose to 138 mg. per 100 ml. Although exudates developed, the papilloedema subsided and over the next month she improved rapidly; blood urea returned to normal, although the hypertension persisted. During this period she unfortunately received 12 grains of barbiturate drugs, and by 5th October, although mentally clear, she had developed a complete flaccid paralysis with slight ptosis and dysphonia. Lumbar puncture on the tenth day of paralysis showed a normal cerebrospinal fluid, but was followed by five severe epileptiform convulsions in one hour.

Transferred to a general hospital (14th October), she was emaciated, with complete flaccid paralysis and limb contractures, B.P. 120/65 and normal fundi (Fig. 3). The urine contained uroporphyrin, porphobilinogen and urobilinogen and the blood urea was 66 mg. per 100 ml. Treatment with prostigmine for one week was without effect. On 30th November, following limb pains and headaches for two days, she suddenly complained of blindness and acute abdominal pain and became confused and restless. B.P. rose to 160/130, the fundi were pale, with the arterioles in spasm, and neck rigidity was marked. Vision returned rapidly to normal, the abdominal pain subsided, but hypertension persisted and the retinal vessels remained in spasm. In December, 1954, there was a further period of confusion, shouting and singing, followed by two days of smiling cheerfulness; then followed a vivid hallucination and a severe epileptiform convulsion. Further episodes of confusion and hallucinations occurred, and in January, 1956, papilloedema was again noted to be present. Scattered retinal exudates and haemorrhages developed and a perimacular "star" was noted in the right fundus. By March, 1956, she could write, feed herself and walk a few steps with assistance, and as hypertension had now been present for four months Serpasil was given, the B.P. falling to normal levels within two weeks. Papilloedema subsided, the exudates appeared to be absorbing, and when discharged in June she weighed 80 lbs., had bilateral footdrop and weakness of the hands. Her urine still contained porphyrins. She is at present well (1957) and able to care for her home and her family without assistance.

(2) *Chronic Cutaneous Porphyria (Cutanea tarda).*

This is also familial, runs a mild course and has a fairly good prognosis, which usually depends on the course of any associated liver disease. It seems to occur particularly in adults in the 40's and 50's, more commonly in males and is characterised clinically by the occurrence of skin photosensitivity and pigmentation, and evidence of liver disease is frequently encountered; histologically there may be cell injury, fatty liver or frank cirrhosis. Kark (1955) considers that all this group have had hepatic disease *before* they developed porphyria and skin manifestations, but his is not a generally accepted view. The skin lesions closely resemble those of erythropoietic porphyria in their photosensitivity, but are milder and do not lead to mutilation. Occasionally lesions may be urticarial or eczemoid in appearance. Discrete pigmented macules may occur and hypertrichosis

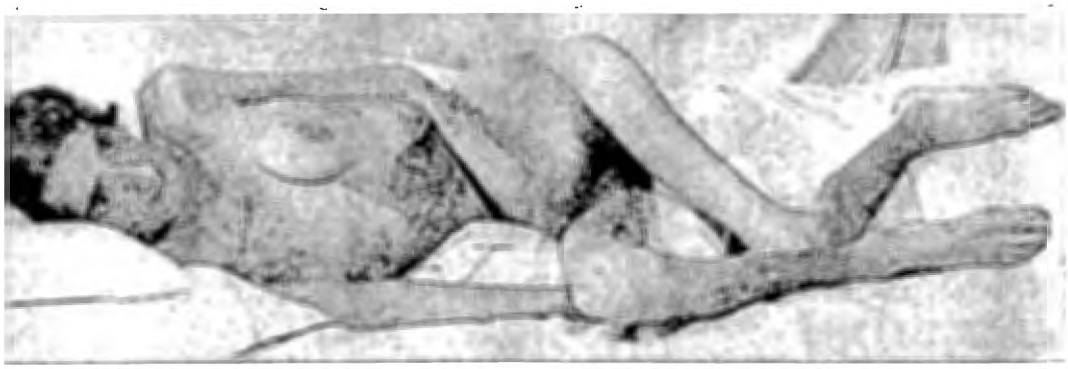


Figure 3.—Case 1 (acute intermittent porphyria). Condition on admission, October, 1954.

may be marked, especially in women. Not uncommonly, diabetes mellitus is an associated finding. Jaundice may be severe and mild abdominal pain may accompany the recurrent crops of skin blisters. They usually pass a reddish urine which contains the same porphyrins excreted in the acute intermittent type, except that porphobilinogen is not present in these cases.

Case 2. Chronic Cutaneous Porphyria. Male aged 42.

In 1942 (aet. 30), after 15 months in Burma, this patient developed a bullous eruption on face and hands. Crops of vesicles, occasionally confluent, appeared, especially on bruised or injured areas where the vesicle might be haemorrhagic. If infected, the vesicles would become scarred and pigmented. This condition recurred daily for three months. In 1951 he experienced a similar episode in Persia, mainly involving the backs of the hands; in 1953 during the summer in England he had a more severe eruption, with desquamation of the backs of the hands. Apart from the skin lesions, there has been no constitutional disturbance. A heavy beer-drinker at week-ends; no family history of similar disorders.

On examination, he was a dark-skinned man with pitted scars about 1 cm. in diameter on forehead and upper face and a few fresh broken bullae on the ears and forehead. The hands showed scattered lesions from scars to fresh bullae, with milia in some of the fresh scars. The skin was slightly thickened.

The urine contained slightly increased urobilinogen, no porphobilinogen, increased coproporphyrin and uroporphyrin I and a small amount of uroporphyrin III. All liver function tests and other investigations were normal. Bone-marrow showed no fluorescence, and on liver biopsy the cells appeared normal, but showed a diffuse red fluorescence under ultraviolet light.

The patient was treated with vitamin B12, 100 micrograms daily for 10 days, and PABA cream, and he appeared to show some improvement.

(3) *"Mixed" or Combined Porphyria.*

This is a term used for those patients presenting with abdominal pain or nervous symptoms, or both, in association with porphobilinogen in the urine, either during the course of chronic cutaneous porphyria or when photosensitivity is in remission. In other cases acute symptoms may have been manifest well before any cutaneous lesions occur. This group emphasises the close relationship between the various subtypes of hepatic porphyria.

Case 3. "Mixed" Porphyria.

March, 1948. One week after Pentothal had been given for a gynaecological operation, Mrs. M. J., aged 48 years, developed abdominal pain, nausea and vomiting, behaved in a rather hysterical manner and was rapidly discharged from hospital. At home, progressive weakness followed, and five weeks after her operation she was readmitted with a complete flaccid paralysis. She then received 35 gr. barbiturate over six weeks, discontinued only when jaundice developed in the seventh week. Liver and spleen were enlarged and tender, the urine contained bilirubin and the serum bilirubin rose to 40 mg. per cent. Jaundice persisted at this level with dark urine and pale stools for six weeks, then slowly subsided over a further four weeks. She then received 15 gr. barbiturate over a further week, and soon after the initial dose manifested a bullous skin eruption. Crops of these bullae appeared daily for three months and then disappeared.

September, 1955: Two months' intermittent epigastric pain and loss of weight, then for one week acute abdominal pain, constipation, vomiting and passage of dark urine. B.P. 150/90 on admission, but this soon rose to 185/120 mm. Hg. and the retinal arterioles were seen to be in marked intermittent spasm. Urine contained uroporphyrin and porphobilinogen; serum bilirubin 1.8 mg. per 100 ml.

Treatment with small doses of Serpasil and Ansolysen orally produced a precipitous fall in B.P. which necessitated the use of a noradrenaline infusion, and on a later occasion Largactil had a similar disastrous effect, also requiring noradrenaline. Following these incidents she had no return of abdominal pain or hypertension and slowly returned to normal. Since then she has had occasional abdominal pain, a mild hypertension and persistent porphyrins in the urine.

Treatment of Hepatic Porphyria.

There is no treatment which will rid the patient with porphyria of his disease. Needless to say, barbiturates and alcohol are contra-indicated. Both ganglion-blocking agents and chlorpromazine have been used with success in cases with abdominal pain, but Case 3 illustrates that these drugs should be used with caution, as individual patients may exhibit undue sensitivity. The value of corticotrophin and cortisone is not established, although in most series of cases so treated one or more have shown a dramatic response. Pethidine, methadone and paraldehyde do not precipitate attacks or aggravate the established episode and may be freely used.

The Fundi in Porphyria.

In reported cases of porphyria, blurred discs have occasionally been noted, while the spasm occurring in the retinal vessels is frequently commented upon. This spasm may be severe and present for many weeks (Case 1) or may merely present as intermittent spasm (Case 3). Papilloedema (Case 1) has not previously been described in this condition. Barnes and Boshoff (1952) have reviewed the ocular lesions in 84 cases, including 46 not of European descent.

In the acute phase of hepatic porphyria, round cotton wool patches were seen which may leave a diffuse granulating or, if they persist longer than three weeks, rounded peripheral blobs of brownish or black pigment. Thin flat striate patches are also seen which leave pale scars with pigment striations.

In the chronic forms of porphyria discrete annular lesions of the choroid are seen, as well as denser clover-leaf lesions spreading out from the disc. While not diagnostic of porphyria, the retinal findings they describe warrant an extensive search for porphyria, especially if they occur in association with suggestive clinical features.

Porphyria in Africans

There is no basic difference in the clinical patterns from those seen in Europeans, and all that has been said previously applies to cases in Africans, but acute intermittent cases are very rare, the vast majority being benign and showing the characteristic skin lesions of chronic cutaneous porphyria.

Two cases of erythropoietic porphyria have been described in South Africa, the first in a 13-year-old African girl referred from a leper institute. She was a typical case with uroporphyrin and coproporphyrin I in the urine, no porphobilinogen and a normal liver histologically and under ultra-violet microscopy.

A recent report from the Northern Sudan describes two cases of erythropoietic porphyria in a brother and sister, the bone-marrow of both showing abundant fluorescing normoblasts under ultra-violet light.

Contrary to usual reports of cutaneous porphyria, there is a predominance of females, although in South Africans of European stock males more frequently show pronounced skin lesions and the females more frequently present with acute attacks. The age incidence shows few cases below 20 years, the majority occurring between 30 and 50 years of age. The condition is only occasionally found to be familial, but as the lesions are mild and few of the reported cases actually presented themselves on account of their porphyria, it seems most unlikely that they would have recognised a similar condition in their relatives.

Presenting Features.—About one-third present with the characteristic "blistering" skin lesions, the remainder attending for reasons bearing no relation to porphyria whatsoever. In over 20 per cent. of cases seen on the Witwatersrand a diagnosis of pellagra had been made, and it should be pointed out that contrary to earlier reports and contrary to what may still be seen in several textbooks, pellagra is not associated with an increase in porphyrin excretions. There were also a fair number of cases diagnosed as pemphigus, dermatitis herpetiformis, hydroea aestivale and Steven-Johnson syndrome.

Skin Lesions.—Some have recurrent attacks; others are continuously affected. The bullae usually occur on the exposed parts, sometimes following slight trauma; they may occur on fingers and hands, and have been occasionally seen on buccal mucosa, tongue, oral pharynx and the mucocutaneous junctions of the lower lip. They vary from a few mm. to several cm. in diameter and contain a clear fluid; occasionally this fluid is reddish or brown. The blisters break to leave a clean raw erosion which takes one to two weeks to heal. The scar resulting from these lesions can be seen for a long time as a hyper- or hypo-pigmented patch. Small milia (epidermal cysts) may be found in the scars, and the new skin may show "tissue-paper" atrophy. If secondary infection has taken place, extensive fibrous scarring may be seen, but one does not see the mutilation which is seen in congenital porphyria. In some cases a velvety warty hyperkeratosis is found over the dorsal surfaces of the two terminal finger-joints which Marshall considers significant of porphyria *if* it occurs in association with bullous lesions.

Nail Lesions.—Subungual blisters lead to softening, loosening, splitting and deformity of the nails. Cracking and peeling occur with atrophy or loss of part of the nail, usually the distal portion.

Hyperpigmentation.—Generalised darkening of the skin over the face and hands is common and may be very marked in some cases. In some of these cases the diagnosis of pellagra may be made. Gelfand (1955) examined the urines of 15 subjects with very dark facial pigmentation and found no porphyrins present.

Hypertrichosis over the temporal and pre-auricular regions is not uncommon, but as soft facial hair is common in Africans this may not be a particularly important feature in diagnosis, the more so as it is never seen without co-existing skin lesions or hyperpigmentation.

Serology.—Of the Johannesburg cases, 50 per cent. showed a positive Kahn reaction, and one presumes this is merely a reflection of the high incidence of venereal disease on the Rand.

Liver Disease.—Over half the cases seen in South and Central Africa have hepatic enlargement and excess urobilinogen in the urine, and on the basis of these features, and on abnormal "liver function" tests, it has been supposed that most African cases show some signs of liver involvement. The Africans in Rhodesia regard the condition as being due to "skokiaan" and Gelfand (1955) found that most of his cases drank it regularly.

If it is an acquired condition, almost certainly alcohol, malnutrition and liver disease are the factors most probably to be incriminated in porphyria in Africans. The study of this condition requires full hepatic function investigation of all these cases, particularly the latent cases of porphyria who have as yet manifested no clinical symptoms of their condition.

SCREENING TESTS FOR THE PORPHYRIAS

Spectroscopy.—The instrument recommended by Barnes is the Beck spectroscope. On spectroscopy the bands of porphyrin and oxyhaemoglobin are essentially similar, two absorption bands in the green, and cannot be differentiated with the ordinary spectroscope.

If the urine is made strongly acid by adding 25 per cent. v/v of concentrated HCl, a porphyrin-hydrochloride spectrum may be seen, with a strong absorption band at 553 mu and a relatively weak band at 597 mu. Oxyhaemoglobin treated in this way yields acid haematin with a broad diffuse band in the red (630-640 mu). Barnes recommends examination of a 5-inch column of filtered urine downward along the axis of the test tube, using untreated urine and after making acid to Congo Red with concentrated HCl acid. He considers this method to be superior to examination under ultra-violet light.

Porphobilinogen (intermittent porphyria; mixed porphyria).

(1) To 1 ml. fresh urine add 1 ml. of Erlich's reagent and mix.
(2) Add 4 ml. supersaturated aqueous solution of sodium acetate and mix.
(3) Test with Congo Red paper, which should give a red reaction.
(4) Add approximately 3 ml chloroform and mix vigorously.
(5) Allow to separate into water and chloroform layers.

Porphobilinogen, if present, will form a brown-red aldehyde on adding Erlich's reagent. This colour will stay in the aqueous layer after mixing with chloroform. Urobilinogen will form a purple-red aldehyde which will migrate into the chloroform layer after mixing. Faint orange or pink reactions should be disregarded or the urine submitted to spectroscopy.

If the urine is rich in urobilinogen one can either transfer the aqueous layer to another tube and shake with more chloroform on several occasions, or the urine can be diluted 1 in 5, acidified with acetic acid and extracted three times with ethyl acetate. Any positive reaction after these procedures is due to porphobilinogen.

Uroporphyrin (intermittent, mixed, delayed cutaneous, congenital).

(1) In the dark, irradiate 10 ml. urine with ultra-violet light. If uroporphyrin is present the urine will fluoresce red or orange-red.
(2) If this is negative, acidify the urine to about pH 4 with acetic acid (approx. 2 ml.), heat for 15 minutes in a water-bath and expose in the dark to ultra-violet light. (Heat at pH 4 converts non-fluorescing porphobilinogen to fluorescing uroporphyrin.)

Coproporphyrin (lead poisoning, secondary porphyrinurias).

(1) Add 2 ml. glacial acetic acid to 10 ml. fresh urine.
(2) Add 30 ml. ether and shake vigorously; allow to separate into two layers.
(3) Examine in the dark under ultra-violet light. A bright red fluorescence in the ether layer indicates the presence of massive porphyrinuria due to ether-soluble porphyrin.

Stools.

(1) (Saunders.) A knife edge of wet stool is dissolved in 3 ml. of a solution of equal parts amyl alcohol, ether and glacial acetic acid. This is placed under ultra-violet light, and if brilliant red fluorescence is obtained it is probably diagnostic of porphyria.
(2) (Barnes.) Loopful of faeces mixed in ½ ml. of glacial acetic acid with a glass rod and then mixed with 2.5 ml. ether. The solids settle rapidly and the supernatant can be examined in ultra-violet light. Normal stool extracts show a greenish fluorescence. Bright pink or red fluorescence indicates porphyrin. The porphyrins from chlorophyll in food can be distinguished by pouring the extract into a clean tube and shaking with 0.5 ml. 1.5 N HCl (15 ml. concentrated HCl dilute to 100 ml. with water). Re-examine in ultra-violet light. Haem porphyrins pass into the acid layer and chlorophyll porphyrins remain in the ether.

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Acknowledgments

I am indebted to Dr. R. R. Hughes, United Liverpool Hospitals, for his encouragement and for permission to publish details of Cases 1 and 3. I am most grateful to Mr. H. D. Barnes, S.A.I.M.R., for the benefit of his wide knowledge of this subject and for his advice on diagnostic procedures. Case 2 is published by kind permission of Dr. S. Gold, Postgraduate Medical School of London.